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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,162	02/08/2000	Judes Poirier	08523/006002	2201

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/31/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/500,162	POIRIER, JUDES	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the response received 18 September, 2002, wherein claims 2 and 16 were canceled without prejudice or disclaimer and claims 1, 3, 6, 8, 9, and 15 amended. Claims 1 and 3-15 are currently under examination. Claims 17-20 stand withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Applicant's arguments and comments have been carefully considered where deemed relevant to the grounds of rejection set forth below.

35 U.S.C. § 120

2. Applicant's claim for domestic priority under 35 U.S.C. § 120 based upon U.S. Serial No. 08/727,637, filed 16 October, 1996, and National Phase application PCT/CA95/00240, filed 26 April, 1995, is acknowledged. These applications disclose methods for assessing Alzheimer's disease (AD) patient responsiveness to cholinomimetic therapy by determining the apoE allele frequency. These applications do not disclose the application of said methods to other neurological disorders. Accordingly, the claims of the instant application are not fully supported under 35 U.S.C. § 112 by these earlier filed parent applications. Therefore, for the purposes of applying prior art, the effective filing date of the instant application becomes **26 December, 1996** (based upon the filing date of the parent application U.S. Serial No. 08/766,975).

35 U.S.C. § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1, 3, 4, and 12 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Roberts *et al.* (1996). Roberts and colleagues disclose a prognostic method for assessing patient outcome in subjects who have sustained head injuries by determining the *apo*E allele load (see p. 3, lines 1-15 and the Example, pp. 4-6). This teaching clearly meets all of the claimed limitations.

35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

6. Claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Roberts *et al.* (1996). As set forth *supra*, Roberts and colleagues disclose a prognostic method for assessing patient outcome in subjects who have sustained head injuries by determining the *apo*E allele load (see p. 3, lines 1-15 and the Example, pp. 4-6). This teaching does not disclose prognostic protocols that also assess the patient's sex. However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was

made to assess various parameters that make up any given patient's profile such as age, sex, past familial involvement, etc., and to incorporate these parameters into the final prognostic protocol. The inclusion of these various factors would allow enable the clinician to make an even more accurate prognosis.

7. Claims 1, 3, 4, 11, 12, and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morris *et al.* (1996) in view of Poirier *et al.* (1995). Morris and colleagues reported that Lewy body dementia (LBD) patients displayed an increased Apo E ε4 allele frequency. LBD is a non-Alzheimer's disease state of the central nervous system that is common to the elderly. This teaching includes all of the claimed limitations except those pertaining to the development of a prognostic protocol. Poirier *et al.* (1995) provide a prognostic protocol for AD patients based upon the *apo*E allele load. The authors noted that AD patients carrying one or two copies of the ε4 allele were less responsive to cholinomimetic therapies. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the methodology of Morris *et al.* (1996) pertaining to a single non-AD neurological disorder to include a prognostic protocol, as taught by Poirier *et al.* (1995). One of ordinary skill in the art would have been motivated to do so because of the strong association between the *apo*E allele load in both AD and LBD. Apoε4 AD patients have decreased levels of choline and choline acetyltransferase (ChAT) activity. Therefore, it would be reasonable for one of ordinary skill in the art to expect non-AD LBD patients carrying the same genetic defect to also respond poorly to cholinomimetic therapy.

35 U.S.C. § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1 and 3-15 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claimed invention is broadly directed toward the use of *apo*E allele determinations to predict the clinical efficacy of a given drug in patients with various neuropathologies. The disclosure describes a method for creating a prognostic protocol for late onset Alzheimer's disease (AD) patients by examining ApoE protein levels. It was reported that individuals carrying one or both copies of the ε4 allele display a poorer clinical outcome as compared to those late onset AD patients lacking the allele. Thus, the claimed invention is enabled only as it applies to late onset AD patients. Appropriately drafted claim language directed toward this embodiment would be acceptable. However, the disclosure is not enabling for claim language directed toward any and all other neurological diseases.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re*

Rainer, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claims are excessively broad and encompass an extremely large genus of disparate neurological disorders. The specification defines neurological diseases (see p. 7) to include the following: Alzheimer's Disease (AD), prion diseases (e.g., Creutzfeldt-Jakob disease), pathologies of the developing brain such as congenital defects in amino acid metabolism (e.g., arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, fragile X syndrome), neurofibromatosis, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, brain injuries due to trauma, and other various pathologies. These sundry disorders all have different pathological determinants (Martin and Longo, 1998; Timchenko *et al.*, 1996; Salvatore *et al.*, 1995; Brouillet *et al.*, 1995). The molecular determinants modulating many of these disorders have been mapped to chromosomal regions unrelated to those of late onset Alzheimer's disease (see Table 363-1, pp. 2294-2303). Moreover, for those neurological disorders with a clear mechanism of disease, most of them do not involve the Apolipoprotein E4. For instance, Creutzfeldt-Jakob disease is caused by a prion protein, Wilson's disease is caused by a defective membrane ATP-ase, amyotrophic lateral sclerosis is caused by a mutant superoxide dismutase (*SOD*1), other forms of amyotrophic lateral sclerosis have been attributed to a mutant neurofilament heavy chain protein, and fragile X syndrome is caused by trinucleotide repeats in the 5' region of the *FMR*-1 gene. Thus, many of these disorders fail to share any genetic linkages or biochemical mechanisms with those of late onset AD and *apo*E allele frequency. Accordingly, the skilled artisan would not consider it reasonable to assert that the *apo*E allele frequency in all these various disorders, many of which do not directly involve Apo E-regulated transport and internalization of

cholesterol and phospholipids, would be predictive of therapeutic responsiveness and clinical outcome. Furthermore, even if the underlying mechanism did affect lipid metabolism, it does not mean that changes in the *apo*E allele load are responsible for the defect. The defect could be present in a downstream or upstream step of the pathway independent of the presence or absence of any given *apo* E allele. The disclosure clearly fails to provide sufficient guidance pertaining to this concern.

2) The disclosure fails to establish any correlation between *apo*E ε4 allele loads and any given neurological disorder other than AD. As noted in point (1) *supra*, the molecular basis for many non-AD neurological disorders remains to be elucidated. For those disorders that have been characterized, most of them do not involve disorders of ApoE-regulated transport and internalization of cholesterol and phospholipids (Martin and Longo, 1998). Thus, the disclosure fails to provide any guidance pertaining to the specificity, sensitivity, and predictive value of measuring the *apo* E allele frequency in any of these disorders.

3) The disclosure fails to provide adequate guidance pertaining to the predictive value of measuring *apo*E allele loads with any particular class of therapeutics. In AD, the *apo*E ε4 allele load is reasonably predictive of patient responsiveness to cholinomimetic therapy. This is not surprising considering the finding that late-onset AD patients have decreased levels of choline and decreased ChAT activity. However, the disclosure fails to provide any guidance pertaining to other suitable therapeutic compounds and the predictive value of measuring the *apo*E allele load in these settings.

4) The disclosure fails to provide any working embodiments involving non-AD neurological disorders. The only example provided involves the relationship between *apo*E allele frequency and cholinomimetic responsiveness in late-onset AD patients. Examples involving non-AD neurological disorders were not provided.

5) The prior art clearly teaches that *apo* E allele frequencies do not correlate with most non-AD neurological disorders. For example, Morris *et al.* (1996) state(abstract, p. 205) that "We have genotyped a large series of clinically and neuropathologically confirmed cases of AD ... **No changes in APO E allele frequencies were found in presenile AD, Parkinson's disease with or without dementia, or in Down's syndrome.**" The authors further reported (abstract, p.205) that "Whilst there appears to be a strong association between the APO E allele and AD and also in LBD, **other related neurodegenerative disorders associated with dementia do not show such a linkage.**" The authors were unable to demonstrate any apparent association between APO E ε4 levels and vascular dementia, Parkinson's disease, alcoholic dementia, and Down's syndrome (p. 207, bottom paragraph). The authors further summarized their studies and reported (p. 212, first full paragraph) that "**Recent studies (Saunders et al., 1993; Pickering-Brown et al., 994; Royston et al., 1994; Martins et al., 1995; Wisniewski et al., 1995) have failed to show an increased ε4 frequency in Down's syndrome patients, and the present results would appear to confirm this**" and that (p. 212, second paragraph) "**Both demented and non-demented Parkinisonian patients showed no significant increase in APO E ε4 frequence, compared to age-matched controls, suggesting that the biological basis of dementia in PD differs from that found in AD and LBD and is not linked to APO E (Benjamin et al., 1994; Koller et al., 1995; Marder et al., 1994).**" Additional studies by Mattila *et al.* (1998) confirmed these findings. The authors reported (abstract, p. 417) that "**The results show that neuropathologically verified PD as such is not associated with increased apoε4 allele frequency.**" It was further noted (p. 419, first paragraph, Discussion) that "our results confirm the findings of clinical series [3, 11, 14] showing no increase in **apoε4** allele frequency in PD. The results of most of the previous

neuropathological series of PD [4, 9, 26] were also similar to those in our study." Earlier work by Rubinsztein *et al.* (1994) was also consistent with these findings. The authors noted (p. 519, abstract and p.523, rt. col.) that "**No significant alteration in the apo E allele distributions was observed in any of these conditions [i.e., multiple sclerosis, Parkinson's diseases, sporadic vestibular schwannomas, and neurofibromatosis], nor did the apo E genotypes correlate with disease severity**" and "**No significant associations were detected with any of the apo E alleles or genotypes with multiple sclerosis or Parkinson's disease. In addition, no relationship was detected between the onset of Parkinson's disease and any apo E genotype. It is thus unlikely that apo E plays an important role in the pathogenesis of these diseases.**" Salvatore *et al.* (1995) also reported (refer to Abstract, page 95) that "**Our results provide further evidence that ApoE is not a risk factor for CJD.**" Finally, Marder *et al.* (1994) also observed (p. 1330, abstract) that "**There was no association between Apoε4 and dementia in the PD patients. We conclude that the biologic basis for dementia in PD may differ from that of AD.**" Thus, the prior art clearly illustrates that the *apo*E ε4 allele is not responsible for many neurological deficits. Therefore, determining the *apo*E allele load would be of no predictive value.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention in a manner commensurate in scope with the claims.

Non-statutory Double Patenting

10. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the

statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

11. Claims 1 and 3-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,935,781. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders and *apo*E allele load determinations while the claims of the '781 patent are directed toward patient prognostic protocols involving patients with cognitive impairments, which is encompassed by neurological disorders. Thus, the claims of the instant application fall within the scope of the claims of the '781 patent and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent.

12. Claims 1 and 3-15 are **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as

being unpatentable over claims 1-14 of copending Application No. 09/865,753. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders while the claims of the '753 application are directed toward prognostic protocol methods involving patients with a non-AD neurological disorder. Thus, the claims of the '753 application anticipate the claims of the instant application and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent. This is a **provisional** obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Correspondence

13. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

14. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be

reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

30 October, 2002

Appendix A: NOTES

- prognosis: to forecast the outcome of a disease.

- APO E gene (chromosome 19) is ~4kb and encodes a 299 aa protein, APO E, APO E is a serum protein that transports triglycerides and cholesterol in the form of very low density lipoproteins (VLDL) or low density lipoproteins (LDL); the frequencies of apo ε3, ε4, and ε2 are 77%, 15%, and 7%, respectively.

- single amino acid changes distinguish these isoforms (ε2 Cys^{158}, ε3 Arg^{158}, Cys^{112}, and ε4 Arg^{112}).

- apolipoprotein E (apoE) regulates the transport of cholesterol and phospholipids during the early phases of reinnervation in the adult brain.

- apoE4 allele has been linked to Alzheimer's disease (AD) suggesting that a dysfunction in lipid transport may be associated with the pathology.

- three major isoforms of apoE (E2, E3, and E4); three common homozygous phenotypes (E2/2, E3/3, and E4/4) and three common heterozygous phenotypes (E2/3, E2/4, and E3/4).

- the frequency of the apoε4 allele is increased in sporadic and late onset AD.

- choline, a rate-limiting precursor of acetylcholine (ACh), is decreased in AD patients; the brain membrane phospholipids phosphatidylcholine (PC) and phosphatidyl ethanolamine (PE) are precursors for Ch production; Ch is released from PC by choline acetyltransferase (ChAT); as apoE4 allele copy number increases, ChAT activity decreases.

- cholinomimetics that are administered to non-apoE4 AD patients, should improve their clinical outcome; AD-E3/3 subjects should be more responsive than AD-E4/3 or E4/4 patients.

- only claims directed toward AD would be allowable

Appendix B: Double-Patenting Issues

L1 ANSWER 1 OF 1 USPATFULL
1999:92499 Apolipoprotein E polymorphism and treatment of Alzheimer's disease.
Poirier, Judes, Boisbriand, Canada
McGill University, Montreal, Canada (non-U.S. corporation)
US 5935781 19990810 <--
WO 9529257 19951102
APPLICATION: US 1997-727637 **19970221** (8)
WO 1995-CA240 19950426 19970221 PCT 371 date 19970221 PCT 102(e) date
PRIORITY: GB 1994-8465 19940427
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a method for the identification of human subjects to be responsive to cholinomimetic therapy comprising determining the absence of apolipoprotein E4 (apoE4) alleles in a biological sample of the patient where the absence of at least one apoE4 allele indicates a predisposition to respond to cholinomimetic therapy and methods of administering cholinomimetics to such identified subjects.

CLM What is claimed is:

1. A method for the identification of human subjects with cognitive impairments to be responsive to a cholinomimetic drug comprising determining the number of copies of apoE4 gene alleles in said subject and wherein the absence of at least one apoE4 gene allele indicates a predisposition to respond to a cholinomimetic drug.

2. A method of treating human subjects with cognitive impairments comprising identifying a subject according to the method of claim 1 and administering a therapeutically effective amount of a cholinomimetic drug wherein administration of the cholinomimetic drug improves cognitive performance.

3. The method of claim 2 wherein said cholinomimetic drug is selected from the group consisting of inhibitors of acetylcholine degradation, inducers of acetylcholine synthesis, acetylcholine agonists or mimics, and muscarinic M2-receptor antagonists.

4. The method of claim 1 wherein the number of copies of apoE4 gene alleles is determined indirectly by determining the presence of apoE2 and/or apoE3 gene alleles using appropriate apoE2 and apoE3 probes.

L2 ANSWER 1 OF 1 USPATFULL
2000:15459 Methods for assessing the prognosis of a patient with a neurodegenerative disease.
Poirier, Judes, Boisbriand, Canada
Nova Molecular Inc., Montreal, Canada (non-U.S. corporation)
US 6022683 20000208 <--
APPLICATION: US 1996-766975 **19961216** (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a method for the determining the appropriate therapy and/or prognosis for a patient diagnosed with a non-Alzheimer's disease (AD) neurological disease based upon the patient's apoE allele load. The invention also provides a method for the identification of human subjects with a non-AD neurological disease that are likely to respond in clinical trials that test pharmaceuticals useful in the treatment of neurological diseases.

CLM What is claimed is:

1. A method for determining the prognosis and ability of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease to respond to therapy comprising the following: a) identifying a patient who has been diagnosed with a non-AD neurological disorder; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) in a prognostic protocol; wherein the presence of at least one apoE .epsilon.4 allele in said patient is indicative of said patient having a poor prognosis of recovery and a decreased responsiveness to therapy.

2. The method of claim 1, wherein said method further comprises obtaining a patient profile.

3. The method of claim 1, wherein said patient is diagnosed with a disease selected from the group consisting of prion diseases, a pathology of the developing nervous system, a pathology of the aging nervous system, nervous system injury, coma, infection of the nervous system, a dietary deficiency, and a cardiovascular injury.

4. The method of claim 3, wherein said prion disease is Creutzfeldt-Jakob disease.

5. The method of claim 3, wherein said patient has been diagnosed with a congenital defect in amino acid metabolism.

6. The method of claim 5, wherein said defect is selected from the group consisting of arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, and tyrosinanaemia.

7. The method of claim 3, wherein said patient has been diagnosed with fragile X syndrome.

8. The method of claim 3, wherein said patient has been diagnosed with a disease selected from the group consisting of neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, and multiple infarcts dementia.

9. The method of claim 2, wherein said patient profile includes a determination of said patient's sex.

10. The method of claim 2, wherein said patient profile includes the patient's genotype.

11. The method of claim 10, wherein said patient's genotype is the presenilin genotype.

12. The method of claim 10, wherein said patient's genotype is the apolipoprotein C1 (apoC1) genotype.

13. A method of characterizing the genotype of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease who is in a clinical trial for the treatment of a non-AD neurological disease comprising the following: a) determining the apolipoprotein E (apoE) allele load of a patient who has been diagnosed with a non-AD neurological disorder through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and b) utilizing the data obtained from step a) in a prognostic protocol.

14. A method for determining the ability of a patient with a non-Alzheimer's disease (non-AD) neurological disease to respond to cholinomimetic therapy comprising the following: a) determining the patient profile of said patient; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) to assess the patient's responsiveness to cholinomimetic therapy; wherein a patient lacking both apoE .epsilon.4 alleles is expected to benefit from cholinomimetic therapies.

REEXAM: **09/865,753**
Methods for assessing the prognosis of a patient with a neurodegenerative disease.
Poirier, Judes, Boisbriand, Canada
Nova Molecular Inc., Montreal, Canada (non-U.S. corporation)
APPLICATION: US 09/865,753 **20010525**
DOCUMENT TYPE: Utility; Reexamination

AB The present invention provides a method for the determining the appropriate therapy and/or prognosis for a patient diagnosed with a non-Alzheimer's disease (AD) neurological disease based upon the patient's apoE allele load. The invention also provides a method for the identification of human subjects with a non-AD neurological disease that are likely to respond in clinical trials that test pharmaceuticals useful in the treatment of neurological diseases.

CLM What is claimed is:

1. A method for determining the prognosis and ability of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease to respond to therapy comprising the following: a) identifying a patient who has been diagnosed with a non-AD neurological disorder; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) in a prognostic protocol; wherein the presence of at least one apoE .epsilon.4 allele in said patient is indicative of said patient having a poor prognosis of recovery and a decreased responsiveness to therapy.

2. The method of claim 1, wherein said method further comprises obtaining a patient profile.

3. The method of claim 1, wherein said patient is diagnosed with a disease selected from the group consisting of prion diseases, a pathology of the developing nervous system, a pathology of the aging nervous system, nervous system injury, coma, infection of the nervous system, a dietary deficiency, and a cardiovascular injury.

4. The method of claim 3, wherein said prion disease is Creutzfeldt-Jakob disease.

5. The method of claim 3, wherein said patient has been diagnosed with a congenital defect in amino acid metabolism.

6. The method of claim 5, wherein said defect is selected from the group consisting of arginosuccinic aciduria, cystathionuria, histidinaemia, homocystinuria, hyperammonaemia, phenylketonuria, and tyrosinanaemia.

7. The method of claim 3, wherein said patient has been diagnosed with fragile X syndrome.

8. The method of claim 3, wherein said patient has been diagnosed with a disease selected from the group consisting of neurofibromatosis,

Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, and multiple infarcts dementia.

9. The method of claim 2, wherein said patient profile includes a determination of said patient's sex.

10. The method of claim 2, wherein said patient profile includes the patient's genotype.

11. The method of claim 10, wherein said patient's genotype is the presenilin genotype.

12. The method of claim 10, wherein said patient's genotype is the apolipoprotein C1 (apoC1) genotype.

13. A method of characterizing the genotype of a patient diagnosed with a non-Alzheimer's disease (non-AD) neurological disease who is in a clinical trial for the treatment of a non-AD neurological disease comprising the following: a) determining the apolipoprotein E (apoE) allele load of a patient who has been diagnosed with a non-AD neurological disorder through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and b) utilizing the data obtained from step a) in a prognostic protocol.

14. A method for determining the ability of a patient with a non-Alzheimer's disease (non-AD) neurological disease to respond to cholinomimetic therapy comprising the following: a) determining the patient profile of said patient; b) determining the apolipoprotein E (apoE) allele load of said patient through genotypic or phenotypic methods, said phenotypic methods including determining the apoE protein isoform; and c) utilizing the data obtained from step b) to assess the patient's responsiveness to cholinomimetic therapy; wherein a patient lacking both apoE .epsilon.4 alleles is expected to benefit from cholinomimetic therapies.